IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of
Anderson
Serial No. 09/994,937
Filed November 28, 2001

Confirmation No. 7327
Group Art Unit 1616
Examiner Abigail Fisher

For SOLVENT SYSTEMS FOR PHARMACEUTICAL AGENTS

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

DECLARATION OF DAVID M. ANDERSON UNDER 37 C.F.R. 1.132

David M. Anderson declares as follows:

1. I am the inventor of the above-identified application. I hold a position in Lyotropic Therapeutics, Inc., the assignee of record of the above-identified application, as Vice President Scientific Affairs. I have read and understand the application, and I have read and understand the office action mailed April 14, 2008. I have also read and understand the references of record.

2. I am an expert in the fields of chemical formulations and drug delivery, particularly as applied to structured fluids including emulsions, liposomes, lyotropic liquids and lyotropic liquid crystals, including reversed cubic and reversed hexagonal phase materials and stabilized dispersions thereof, and the like. As evidence of my expertise, I have attached hereto my curriculum vitae (CV) as **Appendix 1**. I hold the degree of Masters in Mathematics and Ph.D. in Chemical Engineering. I have authored over twenty papers which appear in refereed journals, and I am a highly skilled investigator competent to conduct experiments on structured fluids and to utilize

equipment for properly characterizing the nature of such fluids. Based on my education, training and experience as set forth in the attached CV, I am qualified to provide opinion evidence on the level of skill of one of ordinary skill in the art, and as to what would be obvious or not obvious to one of ordinary skill in the art. In addition, I am qualified and equipped to conduct experiments and to provide test results relating to various pharmaceutical formulations.

3. I have reviewed the prior art cited by the Examiner in the Office Action, and in particular the Landh, Benet and Yau patents cited by the Examiner.

4. Laboratory personnel at Lyotropic Therapeutics and I conducted the following scientific work and obtained the following data in numbered Items 5, 6 and 9. To reduce the amount of work necessary, unless otherwise noted we worked with reversed cubic phase material. The results obtained are applicable to reversed hexagonal phase material as well.

5. We formulated three different cubic phase materials attempting to incorporate paclitaxel for comparison purposes, namely: (i) according to the teaching of the Invention; (ii) according to the teaching of the Invention but without using the fourth component, that is, the essential oil / solubilization agent; and (iii) according to the teaching of Landh.

In sum we found with respect to loadings of paclitaxel, respectively: (i) the loadings in the material of the Invention were high; (ii) cubic phase material incorporating the material simply could not be made according to the teachings of the Invention without the use of the essential oil; and, (iii) the loading of paclitaxel in material according to Landh was comparatively very low.

Formulation (i). Using the poloxamer / spearmint oil / water reversed cubic phase of the Invention, the anticancer agent paclitaxel was successfully solubilized at a concentration of 34 mg/mL (3.4%) in that cubic phase, a loading that would be considered high for a solubilization technology in existence today. This was accomplished by first dissolving the paclitaxel in the spearmint oil, then mixing this

solution with the poloxamer (under the trade name Pluronic P123) and water. In another batch, using Pluronic L122, a poloxamer of even lower HLB [hydrophilic – lipophillic balance] and solubility, a loading of 20 mg/mL was produced, with the reversed cubic phase composition being 2.0% paclitaxel, 23.7% spearmint oil, 23.5% water, and 50.8% L122. In another batch, using a mixture of essential oils and essential oil components, a loading of 42 mg/mL (4.2%) was obtained: the oil mixture was 70% carvone (the dominant component of spearmint oil), 15% strawberry aldehyde, 15% sandalwood oil, with 10% paclitaxel solubilized in the oil mixture, then a reversed cubic phase was prepared by mixing 42% oil/paclitaxel, 18% water, and 40% Pluronic P103. These results are fully consistent with and would be achieved with other of the co-solubilizers and lipid/surfactants identified in the Invention. These cubic phases showed no evidence of precipitation, using in every case visual inspection, polarizing optical microscopy, and differential interference microscopy. Physicians and pharmaceutical industry experts in our company have reasoned that for a home treatment program based on oral paclitaxel, an appropriate effective dose would be approximately 70 mg per day which, using the latter cubic phase, would require only 1.7 grams of cubic phase, easily within the range of a two-capsule dose.

Formulation (ii). The dramatic effect of incorporating essential oils as a fourth component into cubic phases was demonstrated for the case of poloxamer / water / paclitaxel / spearmint by comparing the solubilization of paclitaxel in this cubic phase with and without spearmint oil. The results for this cubic phase with essential oil were given above and were in the range of 20 – 42 mg/mL depending on the exact essential oil or mixture used. When solubilization of only 4 mg/mL paclitaxel was attempted in the binary L122-water cubic phase without the presence of the fourth component essential oil, massive precipitation of drug was observed. This clearly demonstrates that the solubility of paclitaxel in the cubic phase prepared without essential oil is at least less than 4 mg/mL, and probably significantly less, and thus at least an order of magnitude lower than what can be obtained with essential oil as demonstrated in formulation (i).

Formulation (iii). In sharp contrast, and underscoring the highly surprising nature of the above discovery, an attempt to load only 3 mg/mL paclitaxel into the monoolein-water cubic phase of Landh reported in the Landh Examples failed

unequivocally. Six milligrams of paclitaxel and 1.2 grams of high-purity monoolein were dissolved completely in ethanol, and after evaporation of the ethanol a solution of paclitaxel in monoolein was obtained. Then water, 0.8 gm, was added and the mixture stirred for 20 minutes to create a cubic phase. Over the next few hours, the sample gradually became more and more opaque, indicating precipitation of the drug. The next day, DIC microscopy showed the presence of a vast amount of precipitated drug, including large "bird's nests" of entangled needles of paclitaxel, which is seen only when large amounts of paclitaxel precipitate. A photomicrograph of this sample in **Appendix 2** reveals these masses of precipitated drug.

My experience is that this same precipitation occurs in phosphatidylcholine, poloxamer, and monoglyceride cubic phases, at loadings of 3 mg/mL or even lower, when no co-solubilizer is present. Furthermore, the co-solubilizer must be, in addition to a safe (FDA acceptable) excipient, a highly effective solubilizer of paclitaxel, and, aside from water-miscible solvents (which cannot be confined inside the cubic phase), the only such co-solubilizers I have found in many years of experimentation with cubic phase-based solubilization of paclitaxel are those identified in the Invention.

6. The following Table shows select results from voluminous solubilization experiments carried out over years to search for ways to incorporate higher loadings of hard-to-solubilize drugs in cubic and hexagonal phase material, and subsequently to demonstrate the unexpectedly high loadings that can be achieved with reversed cubic phases made from the four component system of the Invention. In the Table, a selection of hard-to-solubilize drugs was solubilized in reversed cubic phase material made from phosphatidylcholine, water, and co-solubilizer in accordance with the teachings of the Invention. The first column in the Table above shows the solubility in soy oil (triglyceride, or fat, from soybeans). This is given for comparison with fat emulsions, which are vehicles currently in used for the solubilization and delivery, including injectable, of a number of water-insoluble drugs, such as propofol, etomidate, and several others. The Invention is surprisingly powerful in terms of solubilization in comparison with that established vehicle. Similar results can be achieved with other of the co-solubilizers identified in the Invention. In every case set forth in the Table, as is reflected

in formulation (ii) of Item 5 of this Declaration, without the use of co-solubilizer the cubic phase incorporated no or significantly lower levels of drug.

Drug	Solubility (mg/ml) in:		
	soy oil	Water	Reversed Cubic Phase Material of the Invention
Nimodipine	**10**	**0.006**	**20**
Paclitaxel	**0.15**	**0.006**	**42***
Mycophenolate mofetil	**3**	**0.039**	**40**
Cyclosporin	**10**	**0.023**	**70**
Alphaxalone	**<1**	**<0.005**	**42‡**
Etomidate	**80**	**0.000045**	**105**
Pramoxine	**<50**	**0.3**	**90+**
Hydrocortisone (Formula 1)	**<0.1**	**0.28**	**3.5**
Hydrocortisone (Formula 2)	**<0.1**	**0.28**	**28≡**
Itraconazole	**<0.5**	**0.000001**	**20**

*Spearmint / sandalwood / strawberry aldehyde mixture, Pluronic 103. ‡ A 50:50 mixture of tocopherol and linalool. + A 4:3 mixture of tocopherol and teatree oil; an earlier reference quotes the aqueous solubility as 0.09 mg/mL. ≡ a 75:25 mixture of clove oil (eugenol) to tocopherol. All solubilities are for the uncharged form of the drug.

Over the years I undertook a tremendous amount of screening of pharmaceutical excipients, alone and in combination with one another. In part, this was guided by my knowledge of molecular packing in reversed liquid crystal systems [see, e.g., P. Strom and D.M. Anderson (1992) Langmuir 8:691; D. M. Anderson, S. M. Gruner and S. Leibler (1988) Proc. Nat. Acad. Sci. 85: 5364; D. M. Anderson, H. Wennerström, U. Olsson (1989) J. Phys. Chem. 93:4532]. In trying hundreds of different combinations of excipients, the inventor discovered a small group that showed unexpected and surprising ability to significantly increase solubility of one or more drugs while maintaining the cubic or hexagonal phase nature of the material. Specifically, unexpected results were

obtained by adding the co-solubilizers identified in the invention (essential oils and a selection of others) to certain cubic phases, namely, solubility of the drug in the cubic phase increased dramatically—as compared to in fat emulsions or in aqueous solution, and in comparison to the cubic phase without the co-solubilizer.

7. The schematic Figure in **Appendix 3** helps to show my conception, based on my knowledge and experience in this field, of the structure of the lipid bilayer in a composition of reversed cubic phase material of the Invention at the molecular scale. It is intended to shed light on the surprising mechanism by which the Invention works and illuminate the characteristics of the co-solubilizers which enable them to create these surprising effects.

As in bilayers generally, the lipid (here, phosphatidylcholine) molecules are assembled in such a way that each polar head group (phosphocholine group) lies preferentially just "above" the "horizontal" plane that divides polar from nominally apolar domains of the bilayer. As this plane cuts the plane of the figure perpendicularly, it appears as a line in the Figure. The apolar tails of the phospholipid, which of course are long hydrocarbon chains, naturally lie on the nominally apolar (or 'hydrophobic') side of the polar-apolar dividing plane. On a larger scale, this polar-apolar dividing plane would actually be seen to curve, so as to form a more complicated surface in space (related to a triply-periodic minimal surface; see D. M. Anderson, H. T. Davis, L. E. Scriven, J. C. C. Nitsche (1990) Adv. Chem. Phys. 77:337-396). The radius of curvature determines the morphology and thus phase of lyotropic liquid crystalline formed. This dividing surface would have a net mean curvature *toward water*, which is a defining feature of the *reversed* form of cubic phase.

Since the phosphatidylcholine-water binary mixture itself, without the essential oil or other co-solubilizer, forms a lamellar phase wherein this dividing surface is indeed planar (flat), it is clear that the essential oil or other co-solubilizer acts to wedge the hydrocarbon tails apart, resulting in a curvature that drives the transformation from lamellar to reversed cubic.

Being low-molecular weight compounds, the molecules making up the co-solubilizer, such as carvone in the case of the essential oil spearmint oil, are prone to

distribute more randomly within the bilayer (due to entropy), although they are water-insoluble so they preferentially diffuse around in the apolar portion of the bilayer. But their chemical character is far different from that of the phospholipid tails. The latter are nothing but hydrocarbon, nothing more polar than an occasional carbon-carbon double bond (typically averaging about 2 such per 18 carbons), whereas the components of the co-solubilizers, including the essential oil, are: (a) decorated with strongly polar groups, such as carbonyls (in the case of carvone), hydroxyls, and other oxygen-laden groups; and (b) of low molecular weight, typically 100-200, and thus inherently better solvents than the lipids themselves, typically 700 or more (and in the thousands, in the case of poloxamers). It is as if an organic solvent were added to the critical region of the bilayer, but without liquefying the phase. Essentially all "organic solvents" in the traditional sense of the term, such as ethanol, DMSO, acetonitrile, etc., will invariably liquefy the cubic phase at very low concentrations, often just a few percent. But essential oils, in spite of their exquisite solubilizing effectiveness, surprisingly can be incorporated into lipid bilayers at levels of 1:2, or commonly even 1:1, weight ratio with the lipid. The same is true of the incorporation into bilayers in the cubic phase comprised of the low-HLB poloxamers.

Consequently, the drug molecule is able to be solubilized in the system, as the polar-decorated low-MW components of the essential oil provide a milieu that can bathe the polar and apolar groups of the drug molecule simultaneously in the decorated bilayer interior. After all, the essential oil is selected based on solubilization of the particular drug within the cubic phase formed by a particular, desired, cubic phase-forming lipid or surfactant. Typically, polar groups on the essential oil molecules are able to satisfy the hydrogen-bonding needs of groups on the drug, and/or other polar-polar interactions, while the hydrophobic groups on the drug are comforted by the apolar groups on both the essential oil and the lipid. The optimal essential oil, in fact, would have just the maximum amount of polarity that would maximize its contribution to drug solubilization (assuming the particular drug has a significant number of polar groups, which is usually the case), but not so much polarity that it gains significant water solubility, and thus partitions significantly out of the bilayer interior. The essential oils and co-solubilizers identified by the Invention are thus characterized in general by: an uneven distribution of

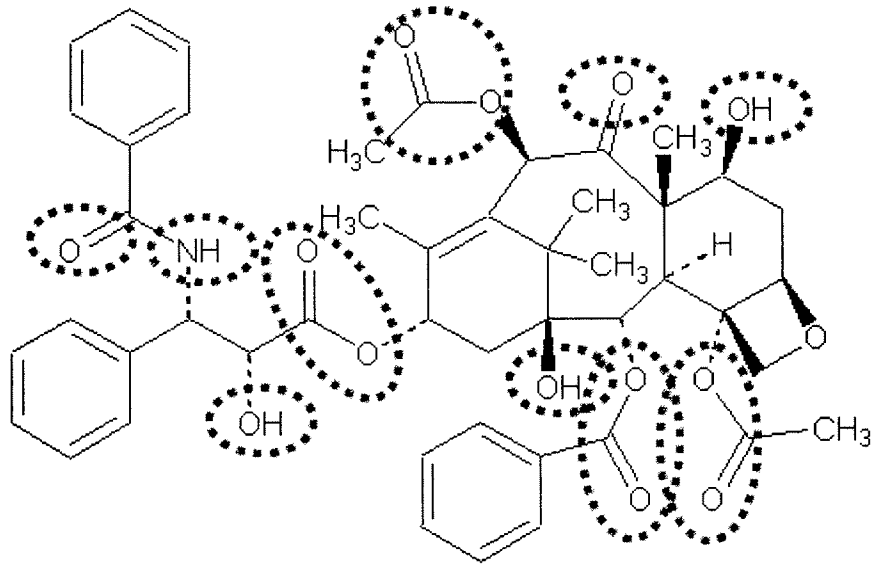
polar and apolar groups; low molecular weights (relatively small molecules); and a relatively high partition coefficient.

Thus the effect of the molecular wedging caused by the introduction of the fourth component of the Invention into the cubic phase bilayer is surprisingly two-fold, and the effects combine to enable the practice of the Invention: first, to create a more favorable local milieu for the drug molecules and thus enable incorporation of hard-to-solubilize drugs; and, second, to increase the radius of curvature of the lipid layer, thus promoting the formation or maintenance of reversed cubic or reversed hexagonal phase material.

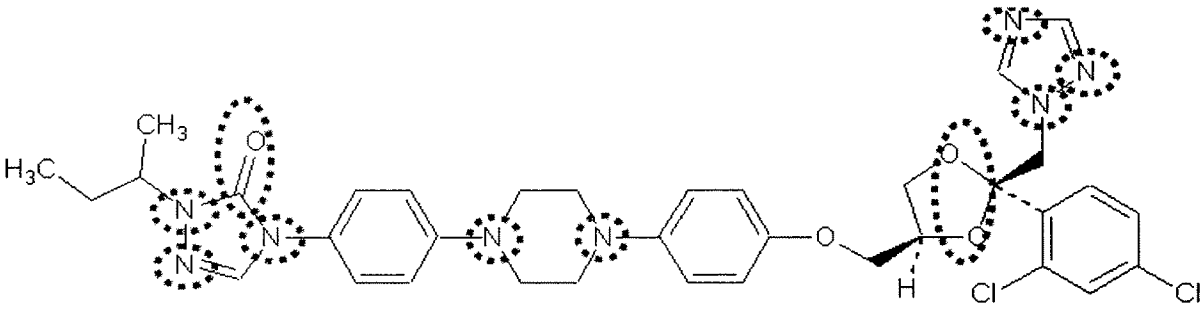
In the case of materials formed with phosphatidylcholine (e.g., Phospholipon 90G, from Lipoid GmbH), which forms a lamellar phase together with water at ambient temperature, the concert of effects at the molecular level springing from the practice of the Invention not only allows the incorporation of drugs at significantly higher loadings, but also allows the formation of the cubic or hexagonal phase material in systems in which such phase otherwise would not form.

8. The following are examples of the molecular structures of important drugs generally considered to be water insoluble, in which various polar groups on the molecule have been highlighted by encircling dotted lines. This reveals that even in a water-insoluble drug molecule, polar groups are frequently sprinkled throughout the molecule. This contrasts with the naïve view that water-insoluble drug molecules are strictly and uniformly hydrophobic. The structures reveal why incorporating co-solubilizer molecules containing polar (and often hydrogen-bonding) groups into the depths of the lipid bilayer as set forth in the Invention has the described effect, and why this success is associated, as identified in the Invention disclosure, with compounds containing at least three polar groups. For ease of visualization, some moderately polar groups, such as aromatic rings, have not been highlighted, though they are certainly more polar than alkyl chains.

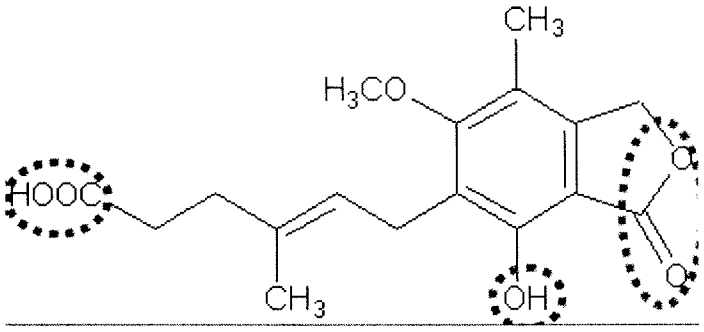
Paclitaxel:



Itraconazole:



Mycophenolic acid:



9. In my laboratory, experiments were performed to determine the effect of adding various essential oils, at a level of 10%, to the cubic phase (monoolein-water) used in virtually all of the Landh Examples. A monoolein-water cubic phase was

prepared by mixing a 60:40 mix of monoolein:water thoroughly, forming a clear cubic phase. This was loaded as 1 gram aliquots into test tubes, and 0.1 grams of essential oil was added to each test tube. The resulting mixtures were stirred, then centrifuged to separate the phases present at equilibrium and to detect any samples which had been transformed to multiphase. Of the ten varied and representative essential oils used, none were taken up fully in a homogenous monoolein-water cubic phase. Liquefication occurred in all ten samples to varying extents. Nine samples were opaque white from excess oil, which was evident in DIC microscopy. The single sample which retained some significant cubic phase material clearly showed the transformation into a two-phase sample. Clearly adding essential oils to the core material of Landh particles is destructive to the material, and thus destructive to the Landh particle.

The monoolein-water reversed cubic phase is not capable of incorporating significant levels of essential oils and retaining homogenous cubic phase morphology. When an essential oil is added to that cubic phase, either the cubic phase is liquefied by the oil, or the cubic phase imbibes a few percent, and the rest splits out as an excess oil-rich liquid phase or other distinct phase. This monoolein-water cubic phase is well known to be very sensitive to liquefaction due to the action of even small amounts of hydrophobic liquids, low-MW solvents, and the like. Indeed, many (and probably most) commercially sourced grades of monoolein are not able to form a cubic phase with water, due to impurities. Because this monoolein-water cubic phase is far more prone to liquefaction than is the phosphatidylcholine-oil-water cubic phase, and the latter is liquefied by a number of essential oils (e.g., palmarosa, bois de rose, citronella, marjoram, lemongrass), it can be expected that a large number of essential oils liquefy the monoolein-water cubic phase of Landh. Since the particles of Landh require a reversed cubic or reversed hexagonal phase liquid crystal at the core, liquefaction of this phase destroys the particles of the Landh invention.

Furthermore, although stabilized Landh particles were not examined in our experiments, it is evident that the addition of an essential oil would tend to destroy the "surface phase" which coats and is required to stabilize the Landh particle. This follows from the fundamentals of lipid phase behavior that addition of a water-insoluble, low-MW liquid, such as an essential oil, will tend strongly to induce a lamellar → reversed

cubic phase transformation, as is seen in the Invention. Since the surface phase of the Landh particle is either a lamellar phase or the closely related L_3 phase, the addition of an essential oil or co-solubilizer of the Invention will tend to make a phase transition in the material back to a reversed cubic phase, thus destroying the surface phase that was created by a reversed cubic phase → lamellar (or reversed cubic phase → L_3) transformation away from the cubic phase in the first place. Alternatively, in Landh particles in which the surface phase is an L_3 phase, addition of an essential oil to this partially-structured liquid phase could readily liquefy or transform the phase to an ordinary lamellar phase, creating either a reversed micellar solution or a structureless liquid. The L_3 phase is well known to have a narrow range of existence both in terms of temperature and composition, and its characteristic bilayer structure is easily broken down.

As discussed throughout the Invention disclosure, varying either the identity or the amount of essential oil or solubilization agent in these lyotropic liquid crystal systems will strongly affect phase behavior, for example, whether the material remains one phase or partially metamorphizes into a second or third phase, and whether cubic, hexagonal or other phase will result. This underscores the fortunate and synergistic nature of the Invention – the same mechanism by which the addition of a fourth component has its effect both enables the incorporation of a difficult to incorporate drug and promotes the formation (or maintenance) of cubic or hexagonal phase material.

10. My background and experience set forth above, and my list of publications in refereed journals, establish my expertise in the field and qualify me to provide evidence on the level of skill of one of ordinary skill in the art to which the above-identified application pertains and to provide evidence on whether or not the invention would have been obvious to one of ordinary skill in the art given the references cited by the Examiner.

In my opinion, one of ordinary skill in the art of lipid based drug delivery would typically have received education leading to the degree of Ph.D. in Chemical Engineering, Chemistry, Biochemistry or a related field. He or she would have likely engaged in research at the Post Doctoral level, and may have been the lead author on a

few articles in refereed journals. He or she would typically have had 5-10 years experience in research and development, and would be familiar with and adept at conducting the type of experiments set forth in this Declaration, and would be adept at preparing phase diagrams. He or she would recognize and understand the differences between emulsions, liposomes, liquid crystalline phase materials (and would recognize differences between cubic phase liquid crystalline phase materials and reversed cubic liquid crystalline phase materials, and hexagonal liquid crystalline phase materials and reverse hexagonal liquid crystalline phase materials), and would know how test for the presence of physically different attributes.

To one of ordinary skill in the art, the teaching of Landh and the Invention would be understood as follows. Landh begins with a three-component cubic phase: polar solvent (usually water), lipid or surfactant (usually monoolein), and drug. Up to this point nothing is new, as the use of cubic phase, and particularly the monoolein-water cubic phase, to dissolve drug has been known for two decades. What is inventive in Landh is the addition of a fourth component, a fragmentation agent (e.g., a high-HLB poloxamer), the purpose of which is to disperse the cubic phase into microparticles of cubic phase coated with another distinct phase created from the cubic phase by a phase transformation. Thus in Landh the fourth component does not promote and is not necessary for the existence of the cubic phase material, but only for the partial destruction of the cubic phase material in order to form the lamellar or L_3 phase coating.

By contrast, the Invention begins with a four component cubic phase: polar solvent (usually water), lipid or surfactant (e.g., low-HLB poloxamer or phosphatidylcholine), co-solubilizer (e.g., spearmint oil), and solubilized drug. In the Invention, either the cubic phase would not form without the co-solvent, or a cubic phase would form but only with very low levels of incorporation of the drug.

While poloxamers are used in both Landh and the Invention, they serve very different functions. In Landh, poloxamers are taught as fragmentation agents. Water soluble poloxamers are preferred. They are introduced to liquefy the cubic phase to form lamellar or L_3 phase material coating phase. In the Invention, poloxamers are one of the types of lipids/surfactants (phosphatidylcholine is another) which form the bulk of the bilayer, the major structural element of the cubic phase. As is well known and discussed

in the disclosure, reversed-type cubic phases can only form with surfactants and lipids of low HLB. (HLB, for "hydrophilic-lipophillic balance", is of central importance in surfactants and lipids, as it measures the relative contributions of water-soluble and water-insoluble parts of the molecule). As stated repeatedly in the specification, only poloxamers of low water-solubility, and thus low HLB, are functional in the Invention. Since an HLB of 10 is considered the dividing line between low and high HLB (as is corresponds to 50:50 hydrophilic: hydrophobic), clearly the poloxamers, and surfactants in general, of use in the Invention are less than 10, and in fact most of the surfactants used in the Examples of the Invention have HLBs close to about 4.

To illustrate the profound difference, if one attempted to use the poloxamers specified in Landh, namely with HLB > 15 (Column 10 lines 32-44), as the lipid/surfactant component of either the Landh reversed cubic phase particle or the reversed cubic phase of the Invention, a reversed cubic phase could not even be created.

In short, Landh first forms a water-insoluble cubic phase using an insoluble lipid such as monoolein, and then disperses it using a high-solubility (high HLB) fragmentation agent such as a poloxamer as a dispersant. By contrast, in the Invention low-solubility (low HLB) poloxamers are used to form the reversed cubic phase. A compound, whether poloxamer or otherwise, that is suitable for making the cubic phases of the Invention will *not* be suitable as a fragmentation agent according to Landh.

This lamellar → reversed cubic phase transformation is integral to the most important embodiments of the Invention, in comparison with the Landh invention. In direct contrast, the expressed purpose of the "fragmentation agents" at the heart of Landh is to induce a transformation *away from* the cubic phase: either reversed cubic → lamellar or reversed cubic → L_3. The purpose, and practice, of the Landh invention is thus antithetical to the Invention.

11. In my opinion, one of ordinary skill in the art would not seek to combine teachings of the Landh and Benet or Yau references as there is no teaching, suggestion or motivation to do so in any of the three references, nor motivation in the problem confronted by the Invention.

12. Phase behavior of lyotropic liquid crystalline systems is subtle and depends upon relative concentrations of ingredients, and the addition of a component can dramatically alter both the phase of material, and the number of phases and structure of the material and particle. It takes a great deal of work to understand and find components and ranges of their use and combinations which yield the desired phase behavior. To discover the small set of compounds which can serve as co-solubilizers as per the Invention and to make the preferred embodiments of the Invention, the Applicant had to find the proper proportion of surfactant or lipid, essential oil and/or dissolution/solubilization agent, drug, and water (or polar solvent) such that this mixture spontaneously formed a single-phase, equilibrium, reversed cubic phase, and this region in composition space is quite small and non-calculable. This region must be then mapped out along with the adjacent phases, in order to determine which cubic phase compositions exist in equilibrium with excess water. Even with the simplifying assumptions of fixed temperature and drug/solubilizer pseudocomponent, this invariably requires the mapping of at least one 3-component phase diagram, each of which requires the preparation and analysis of dozens if not hundreds of samples. The final composition not only must be the desired morphology (reversed cubic, or less preferably, reversed hexagonal phase), but must also maintain sufficient stability to project that the drug will remain in solution throughout the shelf-life of the final product.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

David M. Anderson, Ph.D.

Oct. 14, 2008

Date

Appendix 1

CV David M. Anderson

Lyotropic Therapeutics, Inc., 10487 Lakeridge Pkwy, Ashland, VA
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EDUCATION

Ph. D. Chemical Engineering, University of Minnesota, June 1986.
Advisors: H. Ted Davis and L. E. Scriven; Enhanced Petroleum Recovery/Surfactant Microstructures Group.
Thesis: "Studies in the Microstructure of Microemulsions".

M. S. Mathematics, University of Minnesota, May 1982.

PROFESSIONAL HISTORY

1999 – present: **V.P. Scientific Affairs** at Lyotropic Therapeutics, Inc. Principal scientist, inventor of LyoCell® technology, and leader of research effort focusing on novel injectable and oral drug-delivery systems based largely on lyotropic liquids and liquid crystals, interactions between lipid systems/microparticles and biological systems, and product development. In charge of design, production, and scale-up of new microparticle formulations, and animal testing by supervised laboratory staff and in collaboration with CRO's and industrial partners. Company portfolio includes one product through Phase I clinical study, a second product successfully tested in the pivotal animal model, and 3 other injectable products in pre-clinical development.

1995 - 1999: **Principal Scientist** at SelectRelease, L.C. Developed oral controlled-release formulations based on synergistic combinations of lipids/surfactants and novel crystalline and polymeric coating materials. Particular focus on formulations for intestinal release. Pharmaceutical formulation work with photodynamic therapy agents led to successful animal tests demonstrating sustained release leading to tumor necrosis. Experimental work and oversight of research and development activities, analysis and report/proposal writing, with input into strategic planning, intellectual property and contracting, and technology acquisition.

1991 - 1995: **Assistant Professor, Biomaterials Dept. and Department of Oral Surgery, SUNY Buffalo**; also adjunct faculty member (Research Assistant Professor) in Biophysics and Chemistry Depts. Research centered around controlled-release materials, and nanoporous polymers and hydrogels incorporating a wide range of polymers including novel polymerizable lipids and surfactants. Taught polymer, biophysics, and biomaterials courses. On the faculty of the NSF Industry/University Center for Biosurfaces (IUCB) which focuses on issues of biocompatibility, bioadhesion, tissue compliance, and biofilm characterization. Spearheaded department-wide grant proposals including one for $2.1MM that elicited a joint Army/Navy/DARPA site visit.

1987 - 1991: **Guest Researcher, Univ. of Lund, Sweden**, with Hakan Wennerström and Björn Lindman in Physical Chemistry 1 Dept., a world-renowned department in colloid and interface science. Research focused on lyotropic liquid crystals, and the polymerization thereof. Funded by NFR (Swedish NSF) and by STU (Swedish Board of Technical Development) for first 2 years; after that I independently funded by arrangements with various industries including Costar, Corp., Union Carbide, and Pharmacia LKB. Supervised one graduate student (Ph.D. Thesis March 1992).

1986 - 1987: **Post-doctoral fellow with the Polymer Science and Engineering and the Mathematics Departments of the Univ. of Massachusetts at Amherst**, with E. L. Thomas and David Hoffman. Research focused on block copolymers, primarily the modeling of thermodynamics and morphology in complex 3-dimensional microstructures.

1982 - 1986: **Director of X-ray Scattering Facility at the Univ. of Minnesota**. While a graduate student, responsible for all matters concerning the operation of the lab, which housed a Siemens D-500 Diffractometer with computer interfacing, and a modified Kratky small-angle camera with a position-sensitive detector. Instrument maintenance,

training of users, billing and records, data analysis.

OTHER SKILLS, AFFILIATIONS AND AWARDS.

Awards and societies: Graduation with high distinction; Tau Beta Pi, Phi Kappa Phi; Runner-up in 1993 Niagara Frontier Inventor of the Year Award; Finalist in 1997 Richmond's New Technology of the Year; Runner-up in 1988 "Innovation Cup" invention contest sponsored by a Swedish technical newspaper (Dagens Industri); member American Association of Pharmaceutical Scientists (AAPS), and American Chemical Society (ACS); Strathmore's Who's Who; Virginia Science Resource Network, Virginia Academy of Science, National Directory of Scientific Experts.

Instrumentation skills. TEM/SEM, ultrafiltration (including hardware/system design), small- and wide-angle X-ray diffraction, pulsed-gradient NMR, aerosol monitoring, particle characterization with light scattering as well as aerosol techniques, polarizing, fluorescence and DIC optical microscopy, IR, NMR (chemical shifts), UV, electrophoresis and liquid chromatography. Aerosol generation and characterization expertise includes condensation particle counters, differential mobility analyzers, electrospray nebulizers, together with a strong background in the characterization of submicron/nanoscale particle characterization via a range of techniques. Short course certifications in rheology, DSC, XRD, and laser particle sizers. Excellent skills in optical instrumentation such as microscopes and telescopes including design of new optical measurement techniques.

Mathematics/modeling/computer skills. Strong computing skills ranging from PC's to mainframe supercomputing, including innovative state-of-art graphics dating back to the earliest days of computer graphics. Sophisticated finite element analyses, including 3D graphics representations of solutions, supported by direct analytical calculations including published methods for a wide range of applied mathematics problems relating to nanostructured materials. Analytical and FE solutions of flow patterns, diffusion profiles, scattering/diffraction phenomena, etc. Modeled structure-property relations in polymers. Modeling of thermodynamics, microstructures, spectroscopic and other measurements of complex structures.

SELECTED PUBLICATIONS.

E. L. Thomas, D. M. Anderson, C. S. Henkee, D. Hoffman, "Periodic area-minimizing surfaces in block copolymers", **Nature** 1988, 334, 598-601.

D. M. Anderson, S. M. Gruner and S. Leibler, "Geometrical aspects of frustration in the cubic phase of lyotropic liquid crystals", **Proc. Nat. Acad. Sci**. 1988, 85, 5364-5368.

Pelle Ström and D. M. Anderson, "The cubic phase in the system didodecyldimethylammonium bromide - water – styrene", **Langmuir**, 1992, 8, 691-702.

D. M. Anderson, P. Ström, "Polymerization of lyotropic liquid crystals", in: **Polymer Association Structures: Liquid Crystals and Microemulsions**, 1988, pp. 204-224, ed. M. El-Nokaly, ACS Symposium Series.

D. M. Anderson and H. Wennerström, "Self-diffusion in bicontinuous cubic phases, L3 phases, and microemulsions", **J. Phys. Chem**. 1990, 94, 8683-8694.

D. M. Anderson, H. Wennerström, U. Olsson, "Isotropic, bicontinuous solutions in surfactant-solvent systems: the L3 phase", **J. Phys. Chem.** 1989 93, 4532-4542.

H. Wennerström and D. M. Anderson, "Curvature energies in surfactant microstructures: the difference curvature. Applications to vesicle stability", **Statistical Thermodynamics and Differential Geometry of Microstructured Materials**, Eds. H. T. Davis and J.C.C. Nitsche, Springer-Verlag, 1992.

D. M. Anderson, J. Bellare, J. T. Hoffman, D. Hoffman, J. Gunther and E. L. Thomas, "Algorithms for the computer

simulation of two-dimensional projections from structures determined by dividing surfaces", **J. Coll. Int. Sci.**, 1992, 148, 398-414.

D. M. Anderson and Pelle Ström, "Polymerized lyotropic liquid crystals as contact lens materials", **Physica A**, 1991, 176, 151-167.

D. M. Anderson, "A new technique for studying microstructures: 2H NMR bandshapes of polymerized surfactants and counterions in microstructures described by minimal surfaces", Supplement to **J. Physique**, Proceedings of Workshop on Geometry and Interfaces, Aussois, France, Sept. 1990, C71-1 - C7-18.

D. M. Anderson, D. C. Martin, and E. L. Thomas, "Maximum entropy data restoration using both real and Fourier space analysis", **Acta Cryst.**, 1989 A45, 686-698.

D. M. Anderson, H. T. Davis, L. E. Scriven, "Mean and Gaussian curvatures of the randomly-decorated Voronoi and cubes tessellations", **J. Chem. Phys.**, 1989 91 (5), 3246-3251.

B. Lindman, Kozo Shinoda, U. Olsson, D. M. Anderson, G. Karlström, and H. Wennerström, "On the demonstration of bicontinuous structures in microemulsions", **Colloids and Surfaces**, 1989 38, 205-214.

D. M. Anderson and E. L. Thomas, "Morphology of star diblock copolymers in the strong-segregation limit", **Macromolecules** 1988 21, 3221-3230.

D. M. Anderson and K. Frame, "Teacher access to mentors through professional scientist organizations and the Virginia Science Resource Network", **J. Va. Sci. Ed.**, 2008 2(2):15-24.

Additional book contributions: Geometric Analysis and Computer Graphics, ed. P. Concus, #17 MSRI Series, Springer-Verlag, 1990; Lectures in Minimal Surfaces, J. C. C. Nitsche, Springer-Verlag; NSF Mosaic, "Computer Images in Five Dimensions", ed. W. Kornberg, 1988; Chemical & Engineering News, Aug. 1985; and Islands of Truth, Ivars Pearson, 1992.

PATENTS AND PATENT APPLICATIONS.

Six issued and nine patent applications pending.

TEACHING.

Courses taught.include graduate courses in Biomaterials, Biophysics, and Polymers (University at Buffalo). This included the development of a new graduate Polymers course.

Student supervision includes one PhD and two M.S. students (completed theses/degrees).

INVITED PRESENTATIONS.

Invited Talks at National / International meetings.

American Physical Society meeting, Pittsburgh, PA, March 1994.

Scientific Conference on Chemical and Biological Defense Research, Aberdeen Proving Ground, MD, Dec. 1994 and November 1995.

Asilomar Conference on Polymers, Monterey, Cal., Feb. 1993.

"Workshop on Ordering in Fluids", Amsterdam, Neth., Sept., 1990.

"Geometry and Interfaces", Aussois, Fr., Sept. 1990.

"Liquids at Interfaces", Les Houches, Fr., June 1989.

European Colloid and Interfaces Society annual meeting, Arcachon, Fr., Sept. 1988 (poster).
"Complex and Supermolecular Fluids", Exxon Corporate Research, July 1985 (poster).
Society of Rheology Meeting, Knoxville, Nov. 1984.
Society of Pure and Applied Mathematics, Seattle, July 1984.
Microscopy Society of America annual meeting, Cincinnati, August 1993.
Oak Ridge Conference of the American Association of Clinical Chemists "Pushing the Envelope II", April 2005.

Defense Department. Invited lectures at the Naval Research Laboratories and Army Edgewood Arsenal (1994 and 1995 Annual Conferences on Chemical & Biological Defense Research), in addition to the DoD-sponsored Asilomar and Chem/Biol Defense conferences cited above. Also site-visited for a block grant proposal I P.I.'d, with a 5-year budget of $2.1 million, selected as one of the top 3 among 227 competitive proposals.

University at Buffalo. Invited talks in the Departments of Biophysics, Oral Biology, Chemical Engineering, Chemistry, and the Roswell Park Cancer Institute; also the Western New York Science Forum and the NSF co-sponsored "Nanobiology at Interfaces" symposium.

Other Universities. Invited talks at: Princeton (Physics Dept., at the invitation of Sol Gruner, and Chemical Engineering / Princeton Materials Institute, at the invitation of Bob Prud'Homme); Cornell (Physics, Stanislas Leibler); MIT (Materials Science and Eng., Edwin Thomas); James Madison University (Biotechnology Association); Umea Univ (Biochemistry, Goran Lindblom); U. Lund (Chemical Technology, Bertil Tornell); U. Arizona (Biochemistry, David O'Brien); U. Wash. Seattle (Chem. Eng., Eric Kaler); U. Michigan (Materials Science, David Martin); McMasters (Biochemistry, Materials Research Center); Medical College of Virginia (Division of Neurosurgery, Timothy VanMeter).

VOLUNTEER WORK.

2005-present: Chair, Government Relations Committee, Virginia Section of the American Chemical Society. Working to coordinate ACS member involvement with governing bodies in science education, legislation and budgeting, as well as in student mentoring, equipment procurement for middle and high schools, and changes in science fair rubrics.

Authored an invited paper for the Journal of Virginia Science Education (JVSE) entitled "Teacher Access to Mentors through Professional Scientist Organizations: The Virginia Science Resource Network" (in press).

Judge at Virginia State Science & Engineering Fair, Metro Richmond Science Fair, Virginia Junior Academy of Science fair; presentations at Career Days, SMV Lunch Series, Chemistry Week events, mentor science projects, etc

Advisor to Hanover County Science Curriculum Committee. Advise particularly in the area of science projects, instrumentation, and fairs, as well as textbook and curriculum choices.

Appendix 2

Photomicrograph to accompany Item 5, Declaration of David M. Anderson

Appendix 3 – Schematic of co-solubilizers in Lipid Bilayer